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Stereoselective synthesis of calonectrin

George A. Kraus

Iowa State University, gakraus@iastate.edu

Bruce Roth

Iowa State University

Kevin Frazier

Iowa State University

Masayuki Shimagaki

Iowa State University

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Stereoselective synthesis of calonectrin

Abstract

Several macrocyclic lactones of the trichothecene class of compounds exhibit significant anticancer activity.' A common structural subunit in each of these lactones is the sesquiterpene verrucarol(1). Anguidin (2), a more highly oxygenated analogue, also shows inhibitory activity against several cancers., Calonectrin (3), considered to be the biogenetic precursor to verru~arol,~ has recently been isolated.

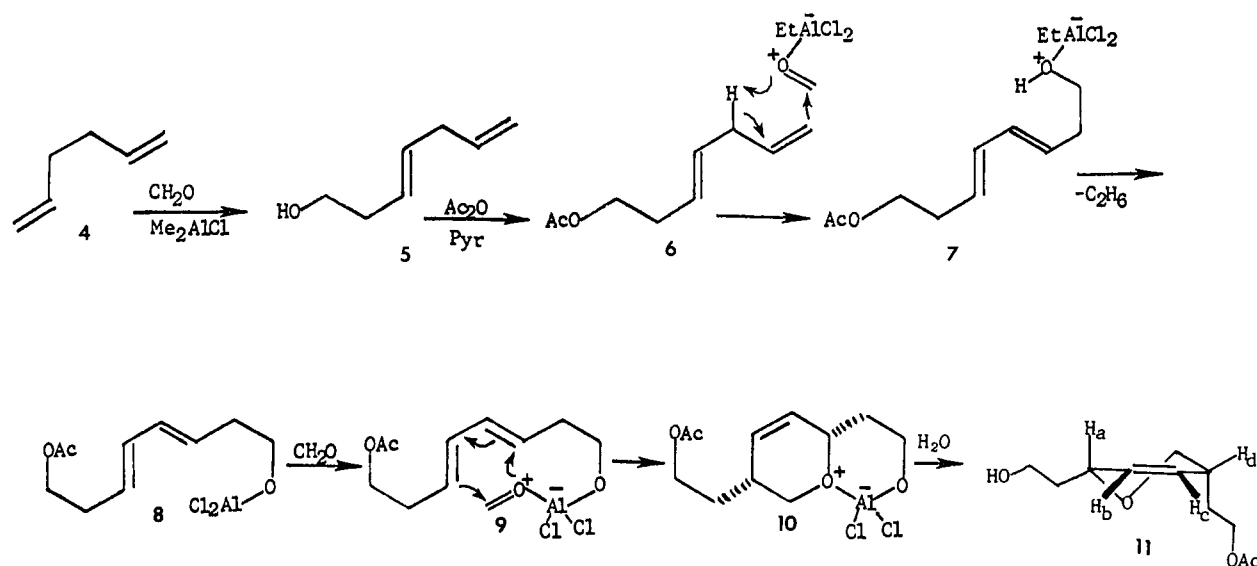
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Scheme II



regioisomer as determined by analysis of the ¹³C NMR spectrum.¹⁰ The acetate of 6 is more basic than formaldehyde and complexes to EtAlCl₂. This complex reacts with CH₂O·EtAlCl₂ at the terminal double bond to give the ene adduct 7, presumably as a 4:1 trans-cis mixture, which loses ethane to give 8. This then complexes to CH₂O to give 9, which undergoes a quasi-intramolecular Lewis acid catalyzed Diels-Alder reaction to give 10. Aqueous workup gives 11. Deactivation of 6 by complexation of Lewis acid to the acetate necessitates the use of EtAlCl₂, which is a stronger Lewis acid than Me₂AlCl with a less nucleophilic alkyl group.

The structure of 11 is assigned based on spectroscopic evidence and its conversion to 15. The cis stereochemistry, which is expected for the Diels-Alder adduct from a trans,trans diene, can be assigned from the coupling constants of the vinylic protons.¹¹ H_b is weakly coupled to the vicinal pseudoaxial proton H_a (≈1 Hz) and to the allylic pseudoequatorial proton H_d (≈1 Hz). Conversely, H_c is strongly coupled to the vicinal pseudoaxial proton H_d (5 Hz) and to the allylic pseudoaxial proton H_a (2 Hz). If the substituents were trans, H_a and H_d would both be pseudoaxial and the coupling constants of the two vinylic hydrogens would be similar.

The regiochemistry of 11 is established by NMR decoupling experiments on the aldehyde 12. Irradiation of the allylic proton α to the oxygen at δ 4.5 collapses the signal from the methylene group α to the aldehyde at δ 2.51 to a broad singlet. The regioselectivity of the reaction depends critically on the solvent. Reaction in methylene chloride gives a 3:1 mixture of 11 and the undesired regioisomer which give a single diol after hydrolysis.

Oxidation of 11 (pyridinium CrO₃Cl, NaOAc) gives the aldehyde 12 in 87% yield. Addition of crude 12 to excess methylmagnesium chloride gives the diol 13. Selective silylation of the primary alcohol (*t*-BuPh₂SiCl, NEt₃, Me₂NC₂H₄N)¹² followed by oxidation of the secondary alcohol (pyridinium CrO₃Cl) gives the methyl ketone 14 in 60% yield from 12. Cis hydroxylation from the less hindered side (cat. OsO₄, *N*-methylmorpholine *N*-oxide)¹³ followed by protection of the diol as the cyclohexylidene ketal (C₆H₁₀O, TsOH, CuSO₄) gives 15 in 82% yield (13% from 1,5-hexadiene). This material is identical with an authentic

sample, kindly provided by Professor Kozikowski, by spectral and chromatographic comparison.⁷ Since 15 has been converted to pseudomonic acids A^{7b} and C^{7a} by Kozikowski, Schmiesing, and Sorgi, this constitutes a formal total synthesis of these antibiotics.

The synthesis of 11 in three steps from 1,5-hexadiene demonstrates the utility of alkylaluminum halide catalyzed reactions of aldehydes and quasi-intramolecular Diels-Alder reactions in organic synthesis.

Acknowledgment. We thank the National Institutes of Health and the Mobil Foundation for financial support and David J. Rodini for conducting preliminary experiments.

Registry No. (±)-1, 80558-54-9; 4, 592-42-7; (*E*)-5, 80502-28-9; (*Z*)-5, 80502-29-0; 6, 80502-30-3; 7, 80502-31-4; 8, 80502-32-5; (±)-11, 80502-33-6; (±)-12, 80514-57-4; (±)-13, 80502-34-7; (±)-14, 80502-35-8; (±)-15, 80558-55-0; (±)-pseudomonic acid C, 80558-56-1.

Stereoselective Synthesis of Calonectrin

George A. Kraus,* Bruce Roth, Kevin Frazier, and Masayuki Shimagaki

Department of Chemistry
Iowa State University, Ames, Iowa 50011

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Several macrocyclic lactones of the trichothecene class of compounds exhibit significant anticancer activity.¹ A common structural subunit in each of these lactones is the sesquiterpene verrucarol (1). Anguidin (2), a more highly oxygenated analogue, also shows inhibitory activity against several cancers.² Calonectrin (3), considered to be the biogenetic precursor to verrucarol,³ has recently been isolated.

Several synthetic approaches to this interesting class of molecules have been reported.⁴ Among these are two total syntheses

(10) All new compounds gave satisfactory spectral and analytical data.

(11) The conformation shown for 11 minimizes 1,3-diaxial interactions. In cyclohexenes, the vicinal coupling constant of the vinylic proton is larger for a pseudoequatorial proton which has a dihedral angle closer to the optimal 0°. The allylic coupling constant is larger for the pseudoaxial proton which has a dihedral angle closer to the optimal 90°. See: Abraham, R. J.; Gottschalk, H.; Paulsen, H.; Thomas, W. A. *J. Chem. Soc.* 1965, 6268.

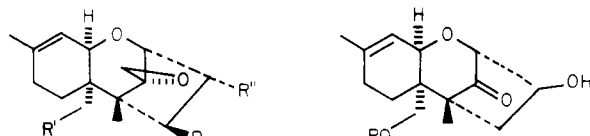
(12) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* 1979, 99.

(13) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* 1976, 1973.

(1) Kupchan, S. M.; Streelman, D. R.; Jarvis, B. B.; Dailey, R. G.; Sneden, A. T. *J. Org. Chem.* 1977, 42, 4221. For biological activity, see: Tamm, C. *Fortschr. Chem. Org. Naturst.* 1974, 31, 63. Bamberg, J. R.; Strong, F. M. "Microbial Toxins"; Kadis, S., Ed.; Academic Press: New York, 1973; Vol. 3, pp 207-292.

(2) Gilgan, M. W. *Arch. Biochem. Biophys.* 1966, 114, 1. Brian, P. W. *Exp. Bot.* 1961, 12, 1.

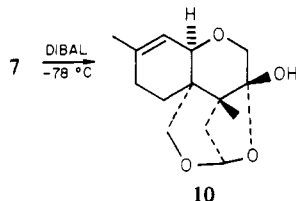
(3) Gardner, D.; Glen, A. T.; Turner, W. B. *J. Chem. Soc., Perkin Trans.* 1972, 2576.



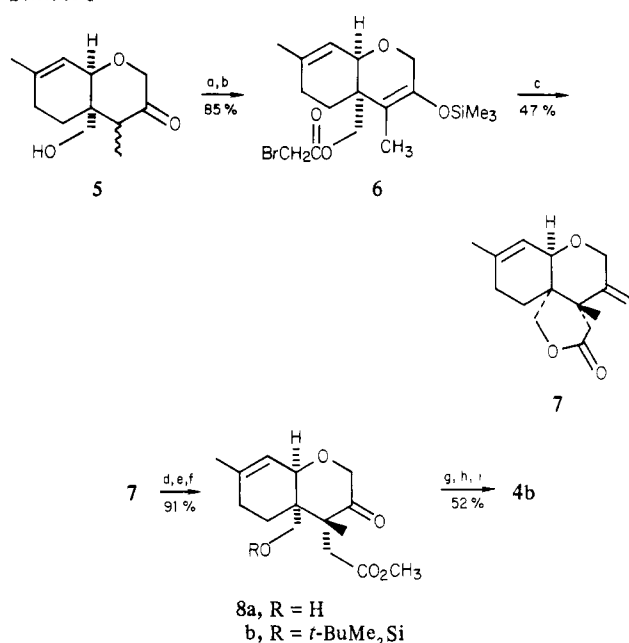
- 1, R = R' = OH; R'' = H
 2, R = R' = O₂CCH₃; R'' = OH
 3, R' = R'' = O₂CCH₃; R = H

- 4a, R = H
 4b, R = *t*-BuMe₂Si

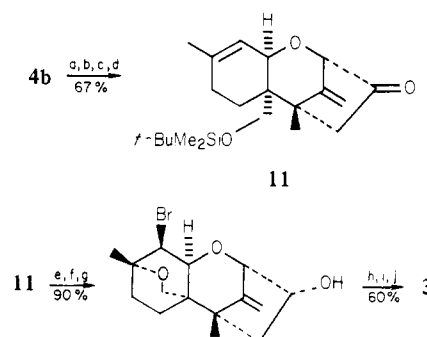
of trichodermol (15-deoxyverrucarol) by Raphael⁵ and Still⁵ and the chemical conversion of anguidin to verrucarol by Fraser-Reid.⁶ Schlessinger has recently reported the total synthesis of **1**.⁷ Synthetic strategies for the tricyclic trichothecene system by Still⁵ and Roush⁸ have focused on the opening of a functionalized [2,2,2] or [3,2,1] bicyclic system. We wish to report the stereoselective synthesis of calonecetrin by an alternate strategy⁹ which produces **4b** via the intramolecular alkylation of enol silyl ether **6** (Scheme I). Ketol **5**, prepared previously in 10% overall yield,¹⁰ was acylated with bromoacetyl bromide at 0 °C. The resulting bromo keto ester was transformed into enol silyl ether **6** by using 0.95 equivalents of iodotrimethylsilane and hexamethyldisilazane in methylene chloride at -25 °C. The isomeric enol silyl ether was also formed in approximately 5% yield. The use of a slight deficiency of iodotrimethylsilane was vital to avoid undesired side reactions.¹¹ The cyclization of crude **6** to keto lactone **7** could be effected with tetrabutylammonium fluoride in tetrahydrofuran. Direct cyclization of the bromo keto ester afforded several products in addition to **7**. The intramolecular delivery of a two-carbon fragment insures the relative stereochemistry and sets the stage for the construction of the tricyclic system. Initially, we envisioned a sequence involving ketone protection, lactone reduction, deprotection, and cyclization to **4a**. Although the hindered ketone in **7** proved to be resistant to ketalization, selective reduction of the lactone to a lactol could be achieved by using 1 equiv of diisobutylaluminum hydride (DIBAL) at -78 °C. Unfortunately, the product, identified as tetracyclic diacetal **10** on the basis of ¹³C NMR absorption at



81.1 and 99.4 and also infrared and high-resolution mass spectroscopy data,¹² could not be induced to cyclize to **4a** (CH₃ONa,

Scheme I^a

^a Reagents: (a) BrCH₂COBr, pyr, 0 °C; (b) Me₃SiI, (Me₃Si)₂NH, CH₂Cl₂, -25 °C; (c) (*n*-Bu)₄NF, THF, -78 → 25 °C; (d) LiOH, H₂O-THF; NaH₂PO₄; (e) CH₂N₂; (f) *t*-BuMe₂SiClO₄, pyr, CH₃CN, 0 °C; (g) LiAlH₄, Et₂O; (h) Me₂SO, ClCOCOCl, Et₃N; (i) NaOCH₃, CH₃OH ↓.

Scheme II^a

^a Reagents: (a) CH₂=CHOEt, PPTS; (b) (Ph)₃P=CH₂, Me₂SO, 70 °C; (c) PPTS, CH₃OH; (d) PCC, CH₂Cl₂; (e) Bu₄NF, THF; (f) NBS, CH₃CN; (g) NaBH₄, CH₃OH; (h) CF₃CO₃H, Na₂CO₃, 0 °C; (i) Zn-Ag; (j) Ac₂O, DMAP, CH₂Cl₂.

CH₃OH ↓; Triton B, CH₃OH ↓). Consequently, keto lactone **7** was hydrolyzed and esterified with diazomethane to the unstable hydroxy ester **8a**. Attempted protection of **8a** with several alcohol protecting groups employing either acidic or basic catalysts resulted in cyclization back to **7**. However, the reaction of **8a** with *tert*-butyldimethylsilyl perchlorate and pyridine¹³ provided **8b** in almost quantitative yield. Reduction of keto ester **8b** with lithium aluminum hydride furnished a diol which in turn was oxidized to a keto aldehyde with Swern's reagent.¹⁴ Reaction of the keto aldehyde with excess sodium methoxide in refluxing methanol¹⁵ afforded tricyclic keto alcohol **4b** in 63% yield. The structure of **4b** was supported by infrared absorption at 3420 and 1760 cm⁻¹. The NMR spectrum indicated that **4b** was a mixture of epimeric alcohols in a ratio of 6:1. The transformation of **4b** to calonecetrin is outlined in Scheme II. Alcohol protection,¹⁶ Wittig reaction

(4) Snider, B. B.; Amin, S. G. *Synth. Commun.* **1978**, *8*, 117. Trost, B. M.; Rigby, J. H. *J. Org. Chem.* **1978**, *43*, 2938. Welch, S. C.; Wong, R. Y. *Tetrahedron Lett.* **1972**, 1583. *Synth. Commun.* **1972**, *2*, 291. Goldsmith, D. J.; Lewis, A. J.; Still, W. C. *Tetrahedron Lett.* **1973**, 4807. Fujimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsuno, T. *Ibid.* **1974**, 2523. Masuoka, E.; Kamekawa, T. *Ibid.* **1976**, 1691. Pearson, A. J.; Rathby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 395. Anderson, W. K. *J. Org. Chem.* **1977**, *42*, 1045. White, J. D.; Matsui, T.; Thomas, J. A. *J. Org. Chem.* **1981**, *46*, 3376.

(5) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989; **1978**, 658. Still, W. C.; Tsai, M. Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. Recently, Dr. Still has synthesized the trichothecene lactone verrucarol.

(6) Fraser-Reid, B. *Tetrahedron Lett.* **1980**, 4549.

(7) Schlessinger, R. H.; private communication.

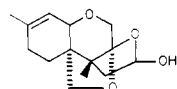
(8) Roush, W. R.; D'Ambra, T. E. *J. Org. Chem.* **1980**, *45*, 3927.

(9) The formation of the tricyclic ring system via intramolecular aldol condensation has also been explored by Raphael⁵ and Fujimoto.⁵

(10) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825. See also: Kraus, G. A.; Frazier, K. J. *J. Org. Chem.* **1980**, *45*, 4820.

(11) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730. Allylic ethers have been reported to react rapidly with iodotrimethylsilane: Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

(12) An alternate structure for **10** that is consistent with our data is shown below. We thank a referee for the suggestion.



(13) Barton, T. J.; Tully, C. R. *J. Org. Chem.* **1978**, *43*, 3649.

(14) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(15) Fujimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsuno, T. *Tetrahedron Lett.* **1974**, 2523.

(16) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

according to the procedure defined by Welch,¹⁷ deprotection,¹⁶ and PCC oxidation provided ketone **11**. Desilylation with tetrabutylammonium fluoride¹⁸ and bromo ether formation¹⁹ were necessary to effect epoxidation of the exocyclic methylene group. Sodium borohydride reduction of the ketone was highly stereoselective since the exo face of the bicyclic [3,2,1] subunit is much more accessible. Epoxidation was accomplished with buffered trifluoroperacetic acid at 0 °C.²⁰ Regeneration of the trisubstituted olefin was effected with zinc-silver couple.²¹ Other reagents such as zinc dust (DMF or THF or CH₃OH) or magnesium (ether, THF) were ineffective. Th acetylation with acetic anhydride and (4-dimethylamino)pyridine in CH₂Cl₂ provided calonecetrin. Synthetic calonecetrin was identical (¹H, ¹³C NMR, IR, MS, TLC) with an authentic sample.

The synthetic route described above is efficient and highly stereoselective. We intend to synthesize anguidin and verrucarol using olefinic ketone **11**.

Acknowledgment. We thank the National Institutes of Health (CA23663) for generous financial support. We thank Professor J. R. Hanson for a generous sample of calonecetrin.

Registry No. **3**, 38818-51-8; **4b**-(α -OH), 80484-01-1; **4b**-(β -OH), 80484-02-2; **5**, 80513-95-7; **6**, 80484-03-3; **7**, 80484-04-4; **8a**, 80484-05-5; **8b**, 80484-06-6; **11**, 80484-07-7; (3 α ,9 α ,10 β)-10-bromo-9,15-epoxy-12-methylenetrithothecane-3-ol, 80484-08-8.

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(19) Corey, E. J.; Pearce, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5843.

(20) Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc.* **1955**, *77*, 89.

(21) Tokoroyama, T.; Matsuo, K.; Kanazawa, R. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3383.

Total Synthesis of Racemic Verrucarol

R. H. Schlessinger* and R. A. Nugent

Department of Chemistry, University of Rochester
Rochester, New York 14627

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The molecular array, verrucarol (**1**),¹ is the sesquiterpene linchpin of a large family of macrocyclic di- and trilactones which possess novel and synthetically challenging structures together with significant antitumor activity.² As part of a larger program directed toward the synthesis of representatives of these macrocyclic systems,³ the construction of verrucarol became desirable.⁴ Herein, we describe a biomimetic formulation of racemic **1** by a route which will ultimately allow its preparation in the required optical form.

We chose as the starting material for construction of **1** the readily available ketonic substance **2**. This material contains two elements required by the structure **1**, namely, the oxygen residue on C₄ and the angular C₁₄ methyl group.⁵ Thus, our initial task

was the transformation of this substance into the keto acid **3**. Degradation of the six-membered ring of **2** was commenced by kinetic deprotonation of the enone with lithium diisopropylamide in THF solution followed by trapping of the enolate with trimethylsilyl chloride. The resulting enol ether was subjected to oxidation with *m*-chloroperbenzoic acid in hexane/*tert*-butyl alcohol at 0 °C yield the α -trimethylsilyloxy enone **4**.⁶ Ozonolysis of **4** in methanol at -78 °C followed by oxidation of the intermediate α -hydroxy acid with sodium metaperiodate/chromium trioxide in acetic acid at 22 °C afforded the keto acid **3** (mp 126-127 °C) in 53% yield from **2**.⁷

Two refractory reactions were then encountered during the elaboration of **3** into the α -methylene lactone **5**, a key synthetic intermediate in our route to **1**. The first of these difficulties was the conversion of **3** into the exocyclic olefin **6**—a reaction which was successful only if the ylide derived from methyltriphenylphosphonium bromide was generated with sodium *tert*-amylate in toluene and the reaction carried out at 110 °C for 12 h. under these conditions, **6** was readily obtained from **3**.⁸ Oxidation of **6** with selenium dioxide and *tert*-butyl hydroperoxide in methylene chloride at 22 °C afforded a mixture of allylic alcohols in which the α -orientated isomer **7** predominated in a ratio of 5:1.⁹ Treatment of this mixture with *p*-toluenesulfonic acid in methylene chloride at 22 °C for 24 h gave the lactone **8** in 55% yield from **3**.¹⁰ Surprisingly, methylenation of **8** to obtain the lactone **5** proved to be the second difficulty encountered in the reaction scheme. A novel and unexpected solution to this problem was discovered, however, during the course of reacting the enolate derived from **8** with monomeric formaldehyde (generated at 160 °C in a flow system). The reactant and reagent were combined at -78 °C and then brought to 22 °C followed by stirring for 14 h; this afforded the α -methylene lactone **5** and not the expected hydroxymethyl lactone.¹¹ Compound **5** was obtained in 62% yield from **8**.

We next faced the problem of spiroannulating the lactone **5** to obtain **9**—a compound which we felt could be readily converted into the target natural product. The Diels-Alder reaction was the obvious choice for this annulation process, and after careful consideration of molecular models of **5**, we were able to convince ourselves that a [4 + 2] cycloaddition between 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene and the methylene lactone would result in addition of the diene from the β surface of the lactone to ultimately afford the unsaturated ketone **9**.¹² Indeed, our view of this reaction course was borne out upon thermal combination of **5** and the above cited butadiene derivative at 140 °C in toluene solvent containing a small amount of methylene blue as a stabilizer. After 48 h of heating followed by removal of the volatiles under vacuum and treatment of the residue with Amberlite IR-120 in methylene chloride for 30 min at 22 °C, we obtained **9** as the sole unsaturated ketone product in 76% yield from **5**.¹³

We had several divergent plans for conversion of **9** into verrucarol. Interestingly, two of these routes were successful, and

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(6) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

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(9) Unbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(10) The β -allylic alcohol could also be converted into the lactone **8** using a procedure described by: Mitsunobu, O. *Synthesis* **1981**, 1.

(11) For excellent reviews on the methylenation of lactones, see: (a) Grieco, P. A. *Synthesis* **1975**, 67. (b) Gammill, R. B.; Wilson, C. A.; Bryson, T. A. *Synth. Commun.* **1975**, *5*, 245.

(12) The use of this diene in total synthesis has been dramatically championed by its originator. For the most recent example of this diene in a synthetic context, see: Danishefsky, S.; Vaughn, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4138. For the definitive series of papers describing the use of this diene, see: (a) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *Ibid.* **1979**, *101*, 6996. (b) Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *Ibid.* **1979**, *101*, 7001. (c) Danishefsky, S.; Harayama, T.; Singh, R. K. *Ibid.* **1979**, *101*, 7008.

(13) The usual reaction conditions, dilute HCl, that bring about conversion of these types of Diels-Alder adducts into enone systems gave mostly the β -methoxy ketone in this instance: see ref 12a.

(1) Gutzwiller, J.; Mauli, R.; Sigg, H. P.; Tamm, Ch. *Helv. Chim. Acta* **1964**, *47*, 2234.

(2) For an excellent review, see: Tamm, Ch. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63.

(3) In our laboratories the natural product vertisporin reported by Minato et al. (Minato, H.; Katayama, T.; Tori, K. *Tetrahedron Lett.* **1975**, 2579) is the current object of our synthetic activities. Recently, we were informed by Professor W. C. Still of Columbia University that he had completed a total synthesis of the related natural product verrucarol A starting from naturally occurring verrucarol. We congratulate Professor Still on this very fine achievement. Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242.

(4) For studies related to verrucarol, see: (a) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 658. (b) Trost, B. M.; Rigby, J. H. *J. Org. Chem.* **1978**, *43*, 2938. (c) Roush, W. R.; D'Ambr, T. E. *Ibid.* **1980**, *45*, 3927. (d) White, J. D.; Matsui, T.; Thomas, J. A. *Ibid.* **1981**, *46*, 3376. For syntheses of trichodermol, see: (a) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989. (b) Still, W. C.; Tasi, M.-Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. For a synthesis of trichodiene, see: Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077.